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PATENT
Attorney Docket No. 02481.0790-02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS

In re Application of:

Michael DORSCHUG et al.

Serial No.: 08/402,394

Filed: March 10, 1995

For: MINI-PROINSULIN, ITS PREPARATION AND USE

Group Art Unit: 1646

Examiner: C. Saoud

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

REPLY BRIEF UNDER 37 C.F.R. § 1.193(b)(1)

Appellants hereby submit in triplicate the following response to the Examiner's Answer dated February 15, 2000.

First, Appellants acknowledge entry of the amendment of claims 40 and 41 and the withdrawal of the rejection of these claims under 35 U.S.C. § 112, first paragraph, based on the comments made at page 5, paragraph #3, of the Examiner's Answer. Therefore, Appellants will not comment on this rejection.

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FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
202-408-4000

Response to Examiner's Arguments

The numbering of the sections below corresponds to the numbering of Section (10) of the Examiner's Answer.

(1) ***Rejection of Claims 21 and 33-36 Under 35 U.S.C. § 103(a)***

The arguments presented by the Examiner in support of obviousness are contradictory and disregard basic tenets of patent law. On the one hand, the Examiner presents numerous statements about the general formula of Markussen, i.e., B(1-29)-$(X_n\text{-}Y)_m$-A(1-21), and that its specific formula, B(1-29)-Ser-Lys-A(1-21), suggests the claimed invention. These statements include: "the selection of Thr for 'X' provides for an insulin precursor which has the native B chain of human insulin because the 'X' is equivalent to the B-30 position of insulin" and "the particular embodiment of B(1-29)-Thr-Arg-A(1-21) is encompassed by Markussen and is very similar to the preferred embodiment of B(1-29)-Ser-Lys-A(1-21)." (Examiner's Answer at pages 11 and 10, respectively, emphasis added). It is also stated that X=Thr and Y=Arg are conservative substitutions of X=Ser and Y=Lys. *Id.*

On the other hand, when presented with an explanation and evidence why this general formula cannot result in Appellants' claimed invention formula, B(1-30)-Arg-A(1-21) without transpeptidation, and therefore, is not a mere conservative substitution, the Examiner contradicts her reliance on the formula of Markussen by saying "Markussen was not cited for its method of making insulin, but only for its methods of making the

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precursor B(1-29)-$(X_n$-$Y)_m$-A(1-21)." (Examiner's Answer at page 12.) It is further stated that "Markussen was not relied upon for the method of obtaining insulin or mono-Arg-insulin. Markussen was relied upon for the teaching of a single precursor peptide chain, fusion proteins, and their cleavage from the precursor . . . ." *Id.*

It is respectfully noted that a prior art reference must be considered for everything it teaches, and the courts have stressed that "[i]t is impermissible within the framework of section 103 to **pick and choose** from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." (emphasis added) *In re Wesslau*, 353 F.2d 238, 241, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965); see also *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448-49, 230 U.S.P.Q. 416, 420 (Fed. Cir. 1986) (holding that district court, by failing to consider a prior art reference in its entirety, ignored portions of the reference that led away from obviousness).

The same circumstances are true here. The Examiner has chosen only specific portions of Markussen et al. that support the argument that the specific species allegedly taught by Markussen would be chosen out of millions of potential compounds and has ignored the overall teachings of the reference, specifically the method required to make that particular species. One cannot ignore the method of making the product taught, if one properly considers the prior art reference for all that it teaches.

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As Appellants discussed in the Appeal Brief at pages 15-18, Markussen argued repeatedly that his invention was to **shorten** the B chain from 30 amino acids to 29 and connect a C-chain comprising $(X_n - Y)_m$ that can be excised upon conversion to insulin. "X" is part of the bridging "C" peptide that is cleaved from the molecule in the process of making insulin and not part of the B chain. No matter what amino acid is chosen, it is not part of the final product. This fact highlights the importance of the method of making the final insulin product from the precursor. According to the method of Markussen, once the C-chain is removed, i.e., X and Y, then the Threonine residue must be added by transpeptidation to yield human insulin.

At page 188 of Appendix C of the Appeal Brief, Markussen emphasizes that the insulin precursor of his invention lacks the B30 Threonine residue present in human insulin stating

> [t]he insulin precursor formula set out in Applicants' claims names the B(1-29) chain, which is a shortened B-chain of human insulin. **The B30 residue (Thr) present in human insulin is not there** . . . . (Emphasis added.)

At page 191 of Appendix C, Markussen continues his argument pointing out that the novelty of his invention is not suggested by the prior art because there is no teaching or suggestion in that art of a **B(1-29) chain**. Rather, Markussen states that the art, Goeddel, "must have the B(1-30) chain", which he argues "in theory" might result if "Applicants' $(X_n$-Y) bridging chain is a peptide which commences with Thr . . . ."

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(Appendix C, sentence bridging 191-192.) However, Markussen argues against the assumption of substituting a Threonine residue for X in his statement that

> [g]ood reason exists for absence of even the narrow (hypothetical) overlap between the proinsulin analogs of Applicants and Goeddel urged by the Examiner. The overlap region must satisfy two different approaches to excision of the bridging chain. The [prior art technique] employs the paired basic amino acid residues that allow excision of the bridging chain in facile fashion. **Applicants employ the transpeptidation technology of Markussen 4,434,898 on the B(1-29)-X_n-Y-A)1-21) [sic - B(1-29)-$(X_n$-Y$)_m$-A(1-21)] peptides.** (Emphasis added.)

Appendix C at 192. Thus, Markussen emphasizes that after cleavage, there must be a transpeptidation reaction performed before the precursor becomes an insulin molecule having a Threonine residue connected to the end of the **shortened** B chain. This is further evidence that one cannot ignore the method of making the insulin molecule, if a Threonine residue is to be present in the product.

Finally, in the Examiner's reasons for allowance of the Markussen '212 patent, upon which Markussen did not comment, it was stated that "[a]pplicants have further pointed out several features which contribute to the superiority of the precursors of the instant invention which are not anticipated or suggested by the [prior art] . . . . **These features are the length of the B chain in the instant invention and the requirement for a bridging chain which does not contain two adjacent basic amino acid residues.**" (emphasis added) (Appendix C at 198.)

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Thus, Markussen was able to overcome the prior art by arguing that the shortened B-chain was what gave his invention its novelty and superiority and argues that a B30 Threonine residue is **never** present in the precursor. The Office cannot now say that "X" is equivalent to the B30 Threonine. This would completely ignore all of the arguments used to overcome the prior art, thereby invalidating the Markussen patent.

In addition, even **if**, for the sake of argument, "X" were Threonine, as the Examiner suggests, it would be cleaved from the molecule in the process of making insulin because "X" is part of the bridging "C" peptide and not part of the B chain. For there to be a Threonine residue present in the final insulin product, it must be added by the transpeptidation reaction in order to achieve human insulin, if one uses the precursor taught by Markussen.

In addition to the problems associated with using the Markussen precursor to arrive at the claimed invention, there are millions of possible choices encompassed by this general formula precursor. The Examiner relies on Grau for the motivation to select the species of Appellants' invention from these millions of compounds. (See Examiner's Answer at page 10.) However, one cannot arrive at the mono-Arg-insulin of Grau ('332) from the precursor of Markussen for the same reasons discussed above and one cannot prepare insulin from the Markussen precursor without transpeptidation. Appellants' method does not require this step.

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Appellants' miniproinsulin has a Threonine residue in the B chain that is not cleaved from the molecule. Appellants' formula is B(1-**30**)-Arg-A(1-21), not B(1-29)-Thr-Arg-A(1-21), as suggested by the Examiner. According to the commonly used nomenclature for insulin precursors, writing the formula as the Examiner has would imply that the Threonine residue is not part of the B-chain and thus would be cleaved from the molecule. However, the B-chain of Appellants' precursor is 30 amino acids long, not 29, the Threonine amino acid residue is part of this chain, and this Threonine amino acid residue is **not** cleaved from the B-chain during the process of making a mature insulin molecule from the precursor of Appellants' invention.

Given that Markussen does not teach a single chain precursor that allows for its cleavage into insulin without transpeptidation and Grau does not teach a single chain precursor, one cannot arrive at Appellants' claimed invention. Regardless of the motivation that might be present in the prior art, one cannot modify the B-chain of Markussen to give B(1-30), especially in view of the prosecution history of the Markussen patent. Thus, for all of the reasons presented above and in Section VIII (B) of the Appeal Brief, Appellants' invention cannot be obvious and the rejection of claims 21 and 33-36 is in error.

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1300 I STREET, N. W.
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(2) *Rejection of claims 25 and 37-38 under 35 U.S.C. § 103(a)*

Claims 25 and 37-38 cannot be rendered obvious for all of the reasons set forth in Section (1) above, and Section VIII (C) of the Appeal Brief. Mai does not solve the deficiencies of Markussen or Grau. Moreover, there is no motivation to combine these references. The mere fact that the Mai reference teaches fusion proteins does not suggest using the specific bridging member of Appellants' invention. The Examiner has improperly used Appellants' specification as a blueprint for deriving the claimed invention from the prior art.

The motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention. See *In re Napier*, 55 F.3d 610, 613, 34 U.S.P.Q.2d 1782, 1784 (Fed. Cir. 1995) ("Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination."); accord *In re Geiger*, 815 F.2d 686, 688, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *In re Laskowski*, 871 F.2d 115, 117, 10 U.S.P.Q.2d 1397, 1399 (Fed. Cir. 1989) ("[t]he mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification") (quoting *In re Gordon*, 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984)); *Sentex Systems, Inc. v. Elite Access Systems, Inc.*, 194 F.3d 1331, 52 U.S.P.Q.2d 1520, ("to invalidate claimed subject

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matter for obviousness, the combined teachings of the prior art references must suggest, expressly or by implication, the improvements embodied by the invention.").

The Federal Circuit has repeatedly warned that the requisite motivation must come from the prior art, not applicant's specification. See *In re Dow Chem. Co. v. American Cyanamid Co.*, 837 F.2d at 473, 5 U.S.P.Q.2d at 1531-1532 ("[t]here must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure"). Using an applicant's disclosure as a blueprint to reconstruct the claimed invention from isolated pieces of the prior art contravenes the statutory mandate of § 103 of judging obviousness at the point in time when the invention was made. See *Grain Processing Corp. v. American Maize-Prods. Co.*, 840 F.2d 902, 907, 5 U.S.P.Q.2d 1788, 1792 (Fed. Cir. 1988).

Mai, at column 3, line 68, in discussing the background of the invention, does state that cyanogen bromide cleaves peptide bonds **after** a methionine residue. There is no teaching that cyanogen bromide cleavage of a fusion protein can occur **befor** the methionine. Later, at column 9, line 6, Mai discloses that factor Xa cleavage sites are preceded by a tetrapeptide, Ile-Glu-Gly-Arg, but then states that the preferred embodiment is Phe-Glu-Gly-Arg. All of the examples involve the fusion protein recA-Glu-Gly-Arg, which incorporates a tripeptide.

There is no teaching or suggestion in Mai of a pentapeptide having the sequence Met-Ile-Glu-Gly-Arg. Nor is there any suggestion that Appellants' fusion protein would

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be cleaved and folded properly using trypsin instead of factor Xa. If the cleavage enzymes to be used are cyanogen bromide and trypsin, nothing in Mai would lead to the selection of Appellants' bridging member. Thus, Appellants find no teaching or suggestion to combine the two disparate forms of cleavage taught by Mai and use a bridging member of Met-Ile-Glu-Gly-Arg absent the knowledge gleaned from Appellants' specification. This rejection, therefore, involves an impermissible piecing together of the teachings of the Mai reference using Appellants' specification as a blueprint.

Often times, particularly with the aid of hindsight, the art appears combinable or modifiable in a manner that will yield the claimed invention. That in itself will not make the resultant modification obvious, however. The art must still suggest the desirability of the modification. See *In re Gordon*, 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984) ("The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification."); see also *In re Mills*, 916 F.2d 680, 682, 16 U.S.P.Q.2d 1430, 1432 (Fed. Cir. 1990).

In *Mills*, the claimed invention covered an apparatus for producing an aerated cementitious composition. The invention had the ability to an create aerated cementitious composition by driving the output pump at a capacity greater than the feed rate. The differential feed and output rates would draw air into the composition and yield a composition with substantially lower density than standard cementitious

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composition mixing ingredients. The single prior art reference taught a mixing chamber having separate input and output pumping motors that operated at various rates. Because the reference contemplated a situation where the rate of the output pump would exceed the rate of the input pump, the Board concluded that the prior art apparatus had the capability of operating in this fashion and to draw air into the mixing chamber to form an aerated composition.

Citing *In re Gordon*, 733 F.2d at 902, 221 U.S.P.Q. at 1127, the Federal Circuit pointed out that "while [the prior art] apparatus may be capable of being modified to run the way [applicant's] apparatus is claimed, there must be a suggestion or motivation in the reference to do so." *In re Mills*, 916 F.2d at 682, 16 U.S.P.Q.2d at 1432. Finding no such suggestion in the art, the court reversed the Board.

Such is the case here. Mai may mention, in one context or another, all of the amino acids included in Appellants' bridging member, but there is absolutely no suggestion or motivation to combine the scattered teachings to arrive at the claimed invention. In view of the fact that the Markussen reference fails to teach the miniproinsulin of the claimed invention and Mai does not teach the bridging member, the rejection of the claimed invention over these references is in error.

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(3) *Rejection of claims 22-23 and 40-41 under 35 U.S.C. § 103(a)*

For all the reasons stated in Section (1) of this Reply Brief and those of Section VIII (D) of the Appeal Brief, claims 22-23 and 40-41 cannot be rendered obvious.

One cannot ignore the mechanism by which one arrives at insulin when addressing a method for preparing insulin. The Examiner states at page 16 of the Examiner's Answer that she does not rely on the Markussen method, but only the generic mini-proinsulin formula for the rejection. This statement is illogical because one cannot ignore the fact that the Markussen precursor cannot be converted into insulin without transpeptidation. To rely on a teaching of the precursor in Markussen in isolation, separated from the teaching of a method of converting this precursor to insulin, impermissibly results in a rejection in which the Examiner has only chosen those portions of the reference that support her rejection, to the exclusion of teachings that teach away from Appellants' claimed invention. As pointed out in Section (1) above, the Federal Circuit in *Bausch & Lomb* reversed the district court's finding of obviousness because it failed to consider a prior art reference in its entirety, ignoring portions of the reference that led away from obviousness. *Bausch & Lomb,* 796 F.2d at 448-49, 230 U.S.P.Q. at 420.

In view of the fact that Markussen does not teach the miniproinsulin of the claimed invention or a method of preparing insulin without transpeptidation, it cannot render obvious the method of preparing insulin from Appellants' miniproinsulin. Grau

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does not teach a single chain precursor or a method of preparing insulin from such a single chain precursor, and there is no teaching in Grau that would overcome the deficiencies of Markussen's precursor to arrive at the claimed invention. Therefore, this rejection is in error.

(4) *Rejection of claims 26-27 and 31 under 35 U.S.C. § 103(a)*

For all the reasons stated in Section (1) of this Reply Brief and Section VIII (E) of the Appeal Brief, as well as the arguments over Mai in Section (2) above, claims 26-27 and 31 cannot be rendered obvious.

The Examiner states at page 7 of the Examiner's Answer that it would have been obvious "to convert the miniproinsulin of Markussen et al. (**having the formula B(1-30)-Arg-A(1-21)**) first to mono-Arg-insulin and then to insulin." However, as discussed in Section (1) above, Markussen does not teach Appellants' formula, but instead teaches the general formula B(1-**29**)-$(X_n$-$Y)_m$-A(1-21). There is no way to convert this precursor into insulin absent a transpeptidation step. Adding this step would defeat the purpose of Appellants' design, namely a miniproinsulin that can be converted into insulin in a single reaction vessel without purification between cleavage steps. Transpeptidation would require an extra purification step, not to mention the extra transpeptidation reaction step itself.

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The Federal Circuit has held that, if a proposal for modifying the prior art in an effort to attain the claimed invention causes the art to become inoperable or destroys its intended function, then the requisite motivation to make the modification would not have existed. See *In re Fritch*, 972 F.2d at 1265 n.12, 23 U.S.P.Q.2d at 1783 n.12 ("A proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for its intended purpose."); *In re Ratti*, 270 F.2d 810, 813, 123 U.S.P.Q. 349, 352 (C.C.P.A. 1959) (holding the suggested combination of references improper under § 103 because it "would require a substantial reconstruction and redesign of the elements shown in [a prior art reference] as well as a change in the basic principles under which [that reference's] construction was designed to operate").

To combine Markussen and Grau in an attempt to render Appellants' invention obvious requires such a substantial reconstruction and redesign of the elements and destroys the basic simplicity of the conversion of Appellants' miniproinsulin to insulin. Moreover, as discussed in Section (2) above, Mai does not teach or suggest the pentapeptide bridging member of Appellants' claimed invention. In view of these remarks, the rejection of these claims is in error.

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FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
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(5) *Rejection of claims 39 and 42 under 35 U.S.C. § 103(a)*

For all the reasons stated in Section (1) of this Reply Brief and Section VIII (F) of the Appeal Brief, claims 39 and 42 cannot be rendered obvious. Therefore, the rejection of these claims is in error.

At page 9 of the Examiner's Answer, it is stated that it would have been obvious to prepare the mono-Arg-insulin from the precursor taught by Markussen and cleave this compound with trypsin as taught by Grau to produce mono-Arg-insulin. Therefore, the Examiner is asserting that mono-Arg-insulin can be obtained from the general precursor disclosed by Markussen. However, the mono-Arg-insulin of Grau does not fall within the generic formula of the starting precursor of Markussen and Markussen's generic formula does not encompass mono-Arg-insulin at any stage of the process. Moreover, the process disclosed by Markussen does not teach the formation of mono-Arg-insulin, or its subsequent conversion to insulin. Thus, contrary to the Examiner's assertion, there is no reason why the skilled artisan would be motivated to use the process disclosed by Markussen to produce insulin via production of mono-Arg-insulin as an intermediate. Mere knowledge of the existence of mono-Arg-insulin does not provide the requisite motivation to modify the process disclosed by Markussen. Mere knowledge of intermediate products would not provide the skilled artisan the motivation or the know-how to modify their reaction procedures to obtain mono-Arg-insulin.

Therefore, the rejection of these claims is in error.

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FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
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202-408-4000

IX. Conclusion

In view of the foregoing arguments, Applicants submit that the rejections of claims 21-23, 25-27, 31, and 33-42 are in error and should be reversed.

By: Carol P. Einaudi
Carol P. Einaudi
Reg. No. 32,220

By: Cheryl Liljestrand
Cheryl Liljestrand
Reg. No. 45,275

Dated: April 14, 2000.

Post Office Address (to which correspondence is to be sent)

Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005
(202) 408-4000

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FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
202-408-4000